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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/753,078	REIFSNYDER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *20-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-49 are pending. Claims 20-49 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-19 have been considered in this Office Action.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 559 632 (the '632 publication; referred to as Diaz-Collier by Applicants).

Response to Applicants argument

TFPI preparations of the prior art must only have less than 12% of one (or more) of the modified species to meet the limitations of the claims.

The examiner first notes that the claims are not limited to TFPI preparations wherein the TFPI has less than 12% of all the modified species. Instead, a TFPI preparation that has less than 12% of any one or more of the species listed is encompassed by the claim. Therefore, for example, a TFPI preparation with less than 12% oxidized species meets the limitations of the claims and it is unnecessary for a

prior art reference to show that all of the modified species of the claims were detected. As discussed below, there is evidence that the TFPI preparation of the '632 publication had less than 12% of any one of or all of the modified species listed in the claims. IN light of this evidence, the examiner has maintained the rejection.

The TFPI of the '632 publication is shown to be "essentially homogenous (>95%)" by more than one measurement

Applicant argues that the '632 publication does not expressly disclose the amounts of oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded species present. This argument has been considered but is not deemed persuasive because the '632 publication provides evidence that the TFPI produced in Example I therein was essentially homogenous (about 95%). The '632 publication states, "[a] reversed phase analysis of TFPI produced by the EXAMPLE I process revealed a single sharp peak (indicating high purity) whereas TFPI produced by the EXAMPLE II process revealed a primary and secondary peak (indicating a significant degree of heterogeneity)" (p. 11, lines 44-47). In addition, the '632 publication indicates that a single symmetrical peak was produced in the cation exchange analysis of the TFPI sample produced by the process of Example I. And, the analysis by EMS revealed 95% homogeneity leaving 5% that could include dimers and/or other "modified" species. Thus, the '632 publication provides three analyses that the TFPI produced therein was highly homogenous and had even less than 5% modified species. Applicants have not provided any evidence that the TFPI of the '632 publication is patentably distinguishable from that of the present application (less oxidized species,

less deamidated?, for example). Applicants have argued that the '632 publication does not mention the extent of oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded TFPI molecules and that the '632 publication does not suggest improving TFPI preparations after refolding to reduce these modified species and only discloses one post-refolding purification step. Applicants add that more recently Gustafson has added purification steps after refolding to improve final product purity and that the present Specification states that the TFPI preparation of the present invention has fewer modified TFPI or TFPI analog species than previous purification methods described in Gustafson. However, this argument does not show that the preparation of the '632 publication had more than 12% modified TFPI species of the claims. Mass Spectrometry can measure molecular masses within an accuracy of 0.01% of the total molecular mass of the sample and therefore would detect any of the claimed modified species. The '632 publication discloses that the electrospray mass spectroscopy (EMS) analysis of the TFPI composition produced therein showed that the TFPI was greater than 95% homogenous. Thus, evidence of record shows that the '632 publication meets the limitations of the claims. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re

Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

The present claims require less than about 12% modified species and the '326 publication teaches a TFPI that is 95% homogenous (5% modified species).

Applicants argue that the Specification shows comparisons of the TFPI preparation made by the method of the present invention and TFPI produced by known processes and that the Specification indicates that the TFPI described in the present Specification contains fewer modified species than TFPI made by the processes of other methods including 6,323,632. This argument has been considered but is not deemed persuasive because the '632 publication shows that the TFPI produced in Example I therein is greater than 95% homogenous and the high level of homogeneity is confirmed by three different tests (EMS, reversed phase chromatography, cation exchange chromatography). Thus, absent evidence to the contrary, the TFPI of the '632 publication has less than 12% modified species.

Restatement of the Rejection

The '632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (p. 8, lines 44-52). Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '632 publication teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was

minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 559 632 (the '632 publication, cited in the Office Action mailed 2/23/06) in view of US Patent No. 6,525,102 (the '102 patent, cited in the Office Action mailed 2/23/06).

Response to Applicants Arguments:

The basis of Applicants argument is that the '632 publication does not disclose that the TFPI prepared therein has less than 12% of all the modified species, oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and misfolded TFPI molecules. First, the claims are not limited to TFPI preparations wherein the TFPI has less than 12% of all the modified species. Instead, a TFPI that has less than 12% of any one or more of the species listed is encompassed by the claim. Therefore, for example, a TFPI with less than 12% oxidized species meets the limitations of the claims and it is unnecessary for a prior art reference to show that all of the modified species of the claims were detected. Second, just because the prior art does not disclose the property of the product does not mean that the product does not have that property. In fact, three different assays indicate that the TFPI produced by the '632 publication is highly homogenous. Mass Spectrometry can measure molecular masses within an

accuracy of 0.01% of the total molecular mass of the sample and therefore would detect any of the claimed modified species. The '632 publication discloses that the electrospray mass spectroscopy (EMS) analysis of the TFPI composition produced therein showed that the TFPI was greater than 95% homogenous. Thus, evidence of record shows that the '632 publication meets the limitations of the claims.

Applicants again argue that electrospray mass spectrometry would not detect dimer formation. This argument has been considered but is not deemed persuasive. As stated in the previous Office Action, it appears that dimer formation is a problem in EMS because *dimers often form during the procedure* and interfere with the interpretation of the results. The evidence presented by Applicants ("Interpreting Electrospray Mass Spectra", p. 7) also indicates that the dimers are detected by the EMS.

> Dimer formation can be a major problem in some analyses. Try to reduce the concentration of the analyte. Often if the concentration is too high *dimers will be observed in the spectrum.* Also, dimers can be reduced by changing some of the settings on the mass spectrometer." (emphasis added, "Interpreting Electrospray Mass Spectra" page 3 of 3 in Evidence provided with the Response filed 5/23/06).

Thus, if there were an error in measuring dimer formation, it would be an erroneously high dimer content rather than missing dimers present in the sample. As shown in the '632 publication, the TFPI was 95% homogenous and possibly higher due to the potential artifact of dimer formation during the measurement procedure. In addition, the claims are not limited to TFPI with less than 12% of the combined modified species but "one or more" of the modified species. Therefore, even if more than 12% of the TFPI molecules were dimers, the TFPI of the '632 publication has less than 12% of oxidized,

carbamylated, deamidated, cysteine adducts, and misfolded TFPI molecules and thus meets the limitations of the claims.

Restatement of the Rejection:

The '632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (p. 8, lines 44-52). Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '632 publication teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the

preparation of the '632 publication is patentably indistinguishable from that of the present claims.

The '632 publication does not teach that the pharmaceutical compositions comprise 20mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, pH 5.5.

However, the '102 patent teaches a preparation comprising TFPI in sodium citrate buffer (Col. 3, lines 41-45) and that adding arginine to a TFPI preparation protects TFPI from aggregation (Col. 6, lines 8-55). The '102 patent also teaches that methionine can be added to TFPI preparations to protect the polypeptide against oxidation (Col. 10, lines 21-43).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the pharmaceutical composition comprising TFPI produced in the '632 publication to contain sodium citrate, L-arginine, and methionine as taught in the '102 patent. The '632 publication teaches a TFPI product that is patentably indistinguishable from that of the claims in its homogeneity. One of ordinary skill in the art would be motivated to add L-arginine and methionine to the pharmaceutical preparation of the '632 publication in order to preserve that homogeneity by preventing aggregation and oxidation during storage. The '102 patent teaches that it is well within the skill in the art to determine the concentration of these agents (Col. 8, lines 27-30). It was also well within the art to determine sodium citrate concentration that would buffer the acidity of L-arginine and lead to greater TFPI stability (a goal of the '102 patent). Thus, one would have been motivated to combine the teachings of the '102 patent and the '632 publication to optimize the TFPI stability after expression and purification.

Conclusions

No Claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The examiner notes that references disclosing the purification of TFPI from natural sources were known prior to the present invention. Naturally occurring TFPI is glycosylated. These preparations are not considered to meet the limitations of the claims because the claims are drawn to TFPI and TFPI analog molecules. The specification defines TFPI as a "non-glycosylated TFPI having the amino acid sequence shown in SEQ ID NO:1" and TFPI analogs as having "a different primary amino acid structure than TFPI as shown in SEQ ID NO:1 (i.e., one or more amino acid substitutions, insertions, deletions, and/or additions)" (p. 9, paragraph [31], lines 1-3).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tues. 10 am-5:30 pm, Thurs. 8 am-5:30 pm, & Fri. 8am to 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bradgon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
January 21, 2007

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER